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**EQUILIBRIUM PERFORMANCE CHANGES PRODUCED BY
ATROPINE IN M. MULATTA AND M. FASCICULARIS**

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NOTICES


This final report was submitted by personnel of the Weapons Effects Branch, Radiation Sciences Division, USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas, under job order 2729-00-06.

When U.S. Government drawings, specifications, or other data are used for any purpose other than a definitely related Government procurement operation, the Government thereby incurs no responsibility nor any obligation whatsoever; and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise, as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.


The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act of 1970 and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.


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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Two species of monkeys were trained to maintain a primate equilibrium platform in a relatively horizontal position by a control stick. Once asymptotic performance was achieved, animals received intramuscularly a saline control injection or 0.105, 0.140, 0.197, or 0.250 mg/kg, in randomized order, of atropine sulfate. The animals' performance was then observed for 3.5 hours. A statistically significant ordering of drug effects was seen, but no differences between species. Atropine produced no effect at the 0.105-mg/kg dose, but marked performance decrements were measured after the 0.250-mg/kg dose.		

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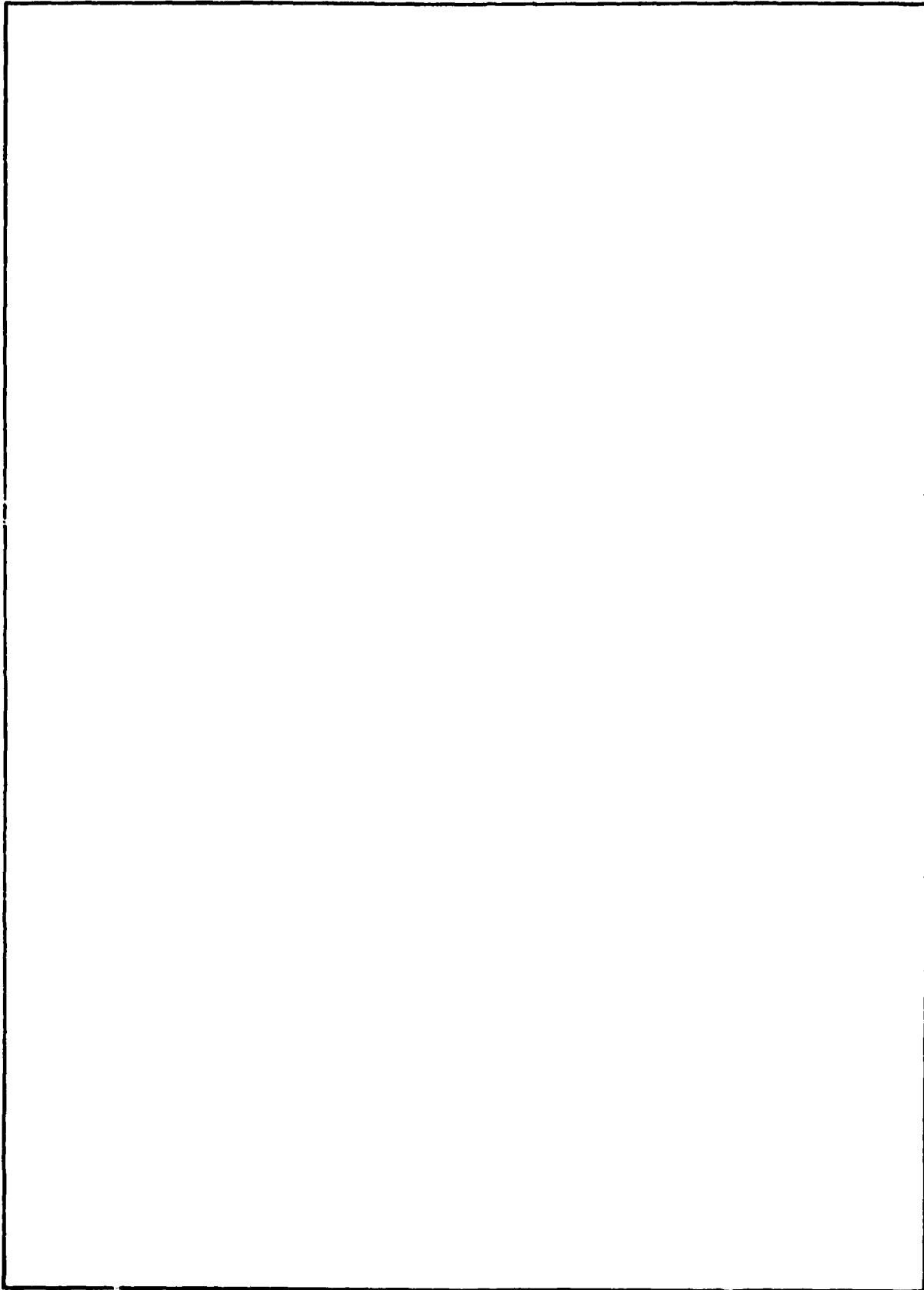
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EQUILIBRIUM PERFORMANCE CHANGES PRODUCED BY ATROPINE
IN *M. MULATTA* AND *M. FASCICULARIS*

INTRODUCTION

In the 1800's the vestibular apparatus was proposed to represent a sixth sense, the sense of space (1). By the turn of the century, Bonnier (2) countered that the input from the vestibular system permits the normal perception of attitude and movement in space only when the sensations of vision and trunk and limb position are taken into consideration. This agrees well with the current interpretation of physiological and behavioral data concerning equilibrium (3).

As might be expected from the number of sensory inputs that contribute to the maintenance of equilibrium, several putative neurotransmitters have been implicated as pharmacological substrates. Many investigations have centered on acetylcholine. They include the pharmacology of motion sickness (4-10), the autonomic nervous system (11), comparative neuroanatomy of the vestibular system (12-15), the neurophysiology of the vestibular system (16-22), and optokinetic and vestibular nystagmus (23-26). The data reported in these studies, taken together, imply that antimuscarinics (like atropine) disrupt equilibrium and other vestibular-related behavior, most likely by depressing neural activity arising from afferent input to the medullary vestibular nuclei. The references cited show that the comparative pharmacology of the vestibular system has been wide ranging, extending virtually throughout the complete vertebrate subphylum. However, systematic study of the behavioral pharmacology of equilibrium has generally been restricted to man; this has primarily centered on the treatment of motion sickness and not on equilibrium behavior per se (i.e., how one orients or moves in space).

Apparently only one report has been concerned with the effects of drugs on equilibrium in the nonhuman primate (27). The authors concluded that the antimuscarinic benactyzine will dramatically degrade performance on a primate equilibrium platform (PEP). Little information is available concerning cholinergic influences on the maintenance of equilibrium, and this has been restricted to rhesus monkeys. In an effort to more precisely describe effects of anticholinergic drugs and to develop additional animal models, the purpose of the present study was to describe the dose-response relationship and the time course of effects of atropine sulfate on PEP performance of two macaque species, *M. mulatta* and *M. fascicularis*.

MATERIALS AND METHODS

Subjects

Six male *M. mulatta* (rhesus) and six male *M. fascicularis* (cynomolgus) monkeys weighing between 2.8 and 8.9 kg were randomly selected and trained. The subjects were experimentally naive prior to onset of the study. During

the course of the study, nondrug PEP performance of one rhesus and one cynomolgus monkey became unstable, thus precluding appropriate treatment comparisons. The data analysis, as a result, is based on the remaining animals, displaying stable baseline performance.

Apparatus

The PEP (illustrated by Yochmowitz et al. (28)) consists of a small restraining chair that was gimballed in a pitch axis in this study. The PEP was driven from the horizontal by a quasi-Gaussian white-noise input signal, low-pass filtered to 0.4 Hz. At its greatest amplitude, the signal would drive the chair to $\pm 30^\circ$ from the horizontal. Affixed to the chair, directly in front of the subject, was a small platform with a control stick that the subject could use to counteract the externally driven movement of the platform.

Training Procedure

A detailed account of training has been described (28). Briefly, the training procedure used a method of approximation. With a mild electric shock (0.2-0.4 mA, a.c., 0.5 s, from a BRS model S-002 shocker) delivered to the feet as a negative reinforcer, the monkeys were first trained to hold the control stick, then to move it in the opposite direction of the pitch of the chair. Once this was accomplished, the amplitude and complexity of the signal were gradually increased to the characteristics described in the "Apparatus" section. Once stable performance was achieved for all animals, the experimental treatments began.

Stable Performance

Animals operated the PEP chair for 4 hours every third day. The performance metric, adjusted root mean square (ARMS), was regressed against time for the 4-hour test session. When six consecutive slopes of ARMS were collected that were not significantly different, as determined by an analysis of variance (ANOVA), an animal's behavior was considered stable.

Adjusted Root Mean Square

The position of the chair, in degrees, was calculated using a PDP-12 computer by sampling the output voltage (V_o) of a follow potentiometer located in the pitch axis of the chair. While the animals worked continuously for 4 hours, platform position (pp) was sampled for 10 minutes, only every other 10 minutes. The sampling period was divided into five epochs, each 102.4 seconds long, with V_o being sampled at 10 samples/second. For each epoch, V_o values were used to compute the following: the average platform position, $pp_2 = (\sum V_o/n)$; the root mean square (RMS) of the platform position, $RMS = (\sum V_o^2/n)^{1/2}$; and the adjusted root mean square,

$$ARMS = RMS^2 - pp^2.$$

Since monkeys were trained to avoid shock that occurred at $\pm 15^\circ$, they were not motivated to seek the 0° position per se. Thus, pp best described the "horizontal" for each animal. However, the variation (ARMS) that occurred around

the pp appeared to be the most useful metric and will be the only one reported. A discussion of these metrics in assessing PEP performance can be found in Yochmowitz et al. (28-30).

Drug Treatments

Atropine sulfate (lot no. 74802) was prepared by the Biomedical Laboratory, Aberdeen Proving Ground, Maryland. All dosages are based on the sulfate form of the drug. Because there was no a priori basis for determining the dosages for the cynomolgus monkeys, the following procedure was used: The dose for the first animal was selected on what was thought would produce mild performance decrements, based on clinical observations. The following animals received either a higher or lower dose, depending on the nature of the response of the preceding animal. However, each animal did receive all treatments, the remainder being administered in randomized order. The doses of atropine were 0.105, 0.140, 0.187, and 0.250 mg/kg. These are one-eighth log dosage increments, starting with an 0.875 log step from 0.014 mg/kg, which is the dose of atropine in a Combopen, the Department of Defense's field injector for treatment of organophosphate intoxication (see Fig. 1 legend for explanation). These doses were similar to those given rhesus monkeys in an unpublished study (27), so for this study both rhesus and cynomolgus monkeys received the same doses. The diluent was 0.9% saline. The control injections consisted of 0.5 cc of 0.9% saline. All injections were intramuscular in the lateral thigh.

Procedure

On a treatment day, two 10-minute data collection sessions occurred prior to drug injection. If the mean and variance of these sessions were within the 95% confidence limits, as calculated from six baseline trials for each animal, then a treatment was administered. If the ARMS values exceeded these limits, the animal was not injected; however, it was then tested every third day until stable performance was reestablished. At least a week intervened between treatments, with each animal being tested once during that time.

RESULTS

Analysis of Adjusted Root Mean Square

As indicated in Figure 1, an orderly progression of performance degradation (increasing ARMS) appears as a function of dose and time for both macaque species. Table 1 presents the mean ARMS values. Table 2 presents an ANOVA¹, which was performed only when the presence of homoscedasticity was determined.

Table 1 shows that no significant difference between species occurred as a function of either dose or time. Because the species x dose and species x

¹ Assistance in the data analysis was provided by the Data Sciences Division of the USAF School of Aerospace Medicine, Brooks AFB, Texas.

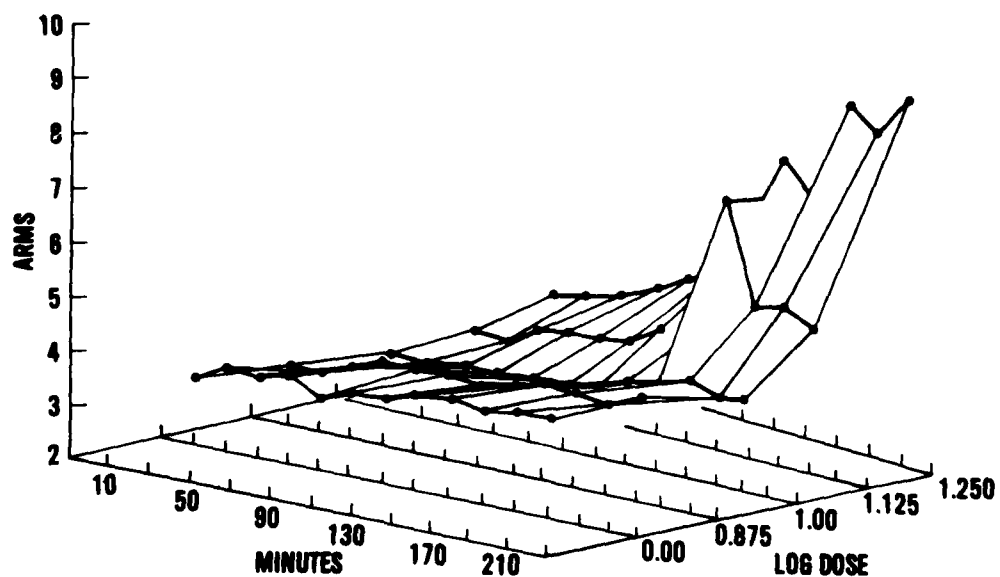
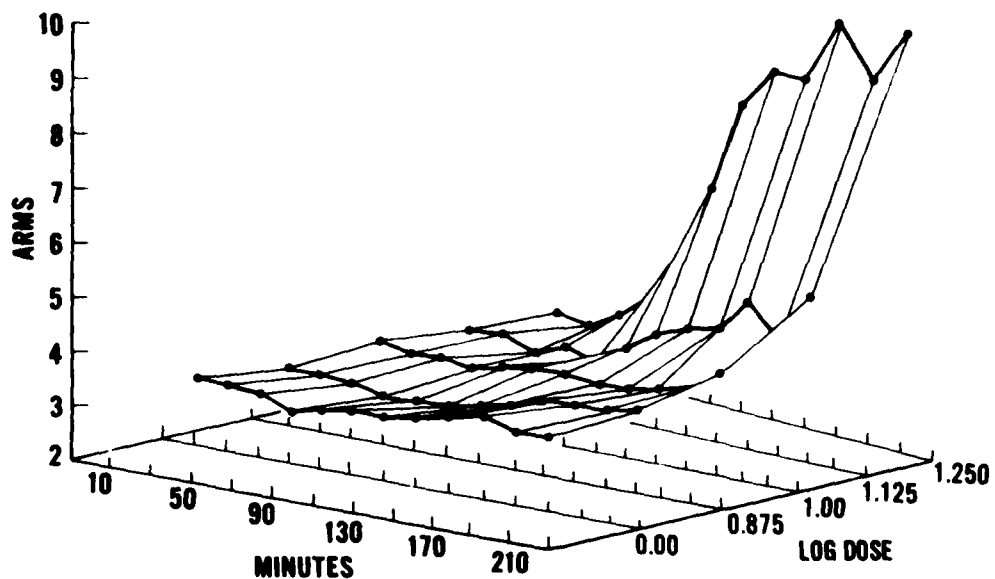


Figure 1. ARMS as a function of time (min) and log dose of atropine sulfate (mg/kg). In a qualitative sense, ARMS values of 3-4 reflect normal behavior, 5-6 indicate noticeable behavioral disruption, and values above 7 reflect dramatic degradation of performance. The bottom portion represents changes for the *M. mulatta*; and the top, for the *M. fascicularis*. N=5 per point. Dose values equal log dose minus Combopen dose; ARMS values are 10-minute means.

TABLE 1. MEAN ARMS VALUES FOR DOSES AND TIME

Minutes	Dosage Increments (Log)					
		0.0	0.875	1.0	1.125	1.250
10	*C	3.2220	3.1520	3.2040	3.0220	2.9760
	**R	3.2880	3.0760	2.8840	3.0900	3.3800
30	C	3.2020	3.1040	3.1360	3.0400	2.9400
	R	3.5020	3.1720	3.0480	3.0540	3.4820
50	C	3.1480	3.0360	3.1240	2.9840	3.2460
	R	3.6740	3.3320	3.0380	3.3840	3.6120
70	C	3.0960	2.9980	3.1520	3.1420	3.7340
	R	3.6380	3.5140	3.1000	3.4560	3.9580
90	C	3.1640	2.9700	3.2240	3.0120	4.7000
	R	3.3960	3.5580	3.1700	3.5020	4.2960
110	C	3.1940	3.0200	3.3460	3.4200	6.1340
	R	3.5780	3.5220	3.1860	3.5580	4.5620
130	C	3.2540	3.1640	3.3640	3.7080	7.7300
	R	3.5480	3.5160	3.3020	3.9720	6.0520
150	C	3.3660	3.2700	3.3940	4.0120	8.4800
	R	3.7220	3.6780	3.4440	4.0740	6.9380
170	C	3.3860	3.4220	3.3780	4.1120	8.4600
	R	3.7640	3.7960	3.6160	6.6800	6.6480
190	C	3.5700	3.4180	3.4980	4.7520	9.6340
	R	3.7240	3.8140	3.7140	4.8980	8.4300
210	C	3.4260	3.4100	3.5020	4.2660	8.7160
	R	3.8840	3.7000	3.6520	4.9000	7.9280
230	C	3.4700	3.5600	3.9200	5.1580	9.7360
	R	3.8260	3.9240	3.7780	4.6820	8.7920

*C = Cynomolgus

**R = Rhesus

TABLE 2. ANOVA ON ARMS VALUES FOR RHESUS AND CYNOMOLGUS MONKEYS
AS A FUNCTION OF TIME AND DOSE OF ATROPINE SULFATE

Source	DF	M.S.O.	F	P
Species	1	0.677	0.01	>0.91
Error Species	8	46.633		
Dose	4	156.303	8.00	<0.0001
Species x Dose	4	6.349	0.32	>0.86
Error Dose	32	19.538		
Time	11	27.512	11.81	<0.0001
Species x Time	11	0.489	0.21	>0.99
Error Time	88	2.330		
Dose x Time	44	9.027	5.05	<0.0001
Species x Dose x Time	44	0.774	0.43	>0.99
Error Dose x Time	352	1.788		

time interactions were not significant, any significant treatment effect produced by time and dose was similar for both species. Nevertheless, both time and dose did produce significant treatment effects and also showed a significant interaction. There is a high probability ($p > .86$) for the tests of all source lines associated with species effects. Two of the interactions had probabilities of .99, suggesting that the estimates of the error terms are too large. This increased error is because the behavior of one animal within each group was more severely disrupted than the others.

A Student-Newman-Keuls Multiple Comparison Test (31) on the mean ARMS scores showed no significant mean differences among the preinjection control sessions. After administration of the 1.250 log dose, the first mean ARMS scores to be significantly different ($p < .05$) from the preinjection values occurred 80-100 minutes post injection. After the 1.125 log dose, the first mean ARMS score to be significantly elevated ($p < 0.05$) occurred 100-110 minutes post injection. No other significant differences were found using this test.

DISCUSSION

Species Differences

The most reliable indicator of equilibrium performance on PEP is the amount of wobble or error (ARMS) that occurs around the average platform position. After injection of various doses of atropine sulfate, no significant differences between *M. mulatta* and *M. fascicularis* were seen for the magnitude of ARMS values.

The first mean ARMS values to be significantly different from predrugged levels occurred between 80 and 110 min after injection. This contrasts sharply with the effect of benactyzine (27), with which ARMS became significantly different from normal behavior within the first 30 minutes after injection. However, the time-course effects of atropine reported here are very similar to those describing the disruption of cognitive effects in humans (32) and antagonism of physostigmine-enhanced central nystagmus (23). Even when atropine is

applied topically to the cerebral cortex, evoked potentials are not maximally depressed for almost an hour (21). These relatively long time delays may merely reflect the slowness of atropine absorption across the blood-brain barrier and diffusion through brain tissue.

The similarity of response of these two monkey species to atropine is noteworthy. Apparently only one other study has examined the effects of a given compound (decaborane, a high-energy fuel) on both species for the same task (33). Unfortunately, the authors did not present the data in a fashion so that any differences, if they did exist, between the species could be tested.

Not only was the response to atropine of these two species similar, so was their behavior after injection of the saline control. This is consistent with ethological and neuroanatomical studies. In addition to the fact that their two territories are often sympatric, they display similar inter- and intra-group behavior, aggressive and mating behavior, and maternal behavior (34,35). The only significant differences that have been noted are their obvious dissimilarity in physical characteristics (35) and, less obvious, some significant differences in location of thalamic nuclei with respect to external cranial landmarks (36). However, these latter differences appear to be attributed to external characteristics of the skull rather than any significant neuroanatomical dissimilarities.

Effects of Atropine on Equilibrium

Based on data collected in this study, no precise statements can be made as to how atropine may bring about changes in ARMS (i.e., equilibrium). It is believed that atropine may alter attentional processes and nociception (36). These might be important considerations, since performance in the PEP is a continuous task and negative reinforcement was used to maintain behavior.

On the other hand, many of the individual factors that are thought to contribute to equilibrium are themselves influenced by cholinergic compounds. For example, electrical activity of neurons in or near vestibular medullary nuclei is depressed by antimuscarinics and antinicotinics and, conversely, is activated by muscarinic agonists (15,16,19,20), though muscarinic influences appear to predominate.

Similarly, anticholinergics can depress, or alter, vestibular as well as optokinetic nystagmus (19,22,24,25) and minimize motion sickness in humans.

Though there may be some nonspecific effect, given the data cited above, the increases in ARMS observed here were probably caused by an atropine-induced disruption of some of the factors that directly contribute to equilibrium; and rhesus and cynomolgus monkeys appeared to be equally sensitive to the atropine sulfate.

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